Classification and Risk Assessment of Chemicals: The Case of DEHP in the Light of REACH

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Abstract: *The process of classification of the toxic properties of hazardous chemicals is not straightforward. Even when the documentation is clear and comprehensive it can take decades before the authorities decide to take action. Moreover, a classification is always on trial because new scientific knowledge can lead to reclassification. It is not easy to understand the politics of the regulatory game because issues other than scientific results set the agenda. Further, the economic consequences for the chemical industry and society are always taken into consideration before risk reduction strategies for hazardous chemicals are decided and implemented. The present paper describes the case of the plasticizer DEHP, a chemical that is still not fully regulated in accordance with its hazardous properties and its classification as a reproductive toxicant. DEHP has been downgraded with regard to carcinogenicity but is now classified as toxic for reproduction and development. This new classification worries the producers and is still on trial, because it brings DEHP on the list of chemicals that are carcinogenic, mutagenic or toxic for reproduction (CMR substances), which is important in the light of the future implementation of REACH, the new EU law on registration, evaluation and authorisation of chemicals. CMR substances will need an authorization for their specific use, and therefore the classification of DEHP as toxic for reproduction is extremely important for producers as well as users because it probably will demand a stricter regulation than seen hitherto.*

Keywords: Classification, risk reduction, carcinogenic, peroxisome proliferation, reproductive toxicity, REACH, regulation of chemicals

Abbreviations:

AGD:	Anogenital distance
Bw:	Body weight
CMR:	Carcinogenic, mutagenic and toxic to reproduction
DEHP:	di(2-ethylhexyl)phthalate
ECPI:	European Council for Plasticizers
IARC:	International Archives of Cancer
Kow:	Partition coefficient, octanol/water
MEHP:	Mono-2-ethylhexyl phthalate
MOS:	Margin of safety
NOAEL:	No observed adverse effect level
PP:	Peroxisome proliferation
PVC:	Polyvinyl chloride
REACH:	Registration, evaluation and authorisation of chemicals
WHO:	World Health Organization

1. Introduction

The aim of Directive 67/548/EEC (EEC 1967) on the classification, packaging and labelling of dangerous substances is to protect consumers and workers against the impact of hazardous chemicals which are placed on the EU market. The directive has been amended several times (EU 2001). According to the directive, the toxicity of a chemical can be classified under different categories and thereafter labelled with risk symbols and risk and safety phrases. About 5000 chemicals are classified as dangerous and registered in the EU classification system. When a chemical is registered it indicates that it belongs to a family of dangerous substances and when traded it should be handled with care in accordance with instructions given on the required label. Chemicals which are carcinogenic or toxic for reproduction belong to risk categories of high concern, because such substances often show effects after long-term exposure to low concentrations and some of them are banned or phased out.

DEHP (*di(2-ethylhexyl)phthalate*), the most used plasticizer in PVC products, has an interesting classification history. For some years, it was a suspected human carcinogen and classified as possibly carcinogenic to humans (category 2) by the United States Environmental Protection Agency and the International Archives of Cancer (WHO 1992). But recently, DEHP was re-evaluated by IARC (2000), where after it was downgraded and declared to be no classifiable in terms of carcinogenicity to humans (category 3). Furthermore, for many years, DEHP was suspected as being toxic for reproduction (Thomas et al. 1984), but without being classified in this category, and in the 1990s, DEHP was also suspected to have an estrogenic effect. However, new studies have supported the hypothesis that DEHP can harm the reproductive system due to an antiandrogenic effect (Gray et al. 2000), and these findings have placed the chemical on the EU list of dangerous substances, where it is now classified as a substance which may be regarded as if it impairs fertility and can cause developmental toxicity in humans (category 2) (EC 2001).

Box 1

Criteria for Classification of Carcinogenic Chemicals

Category 1: Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer

Category 2: Substances, which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer generally on the basis of: appropriate long-term animal studies - or other relevant information.

Category 3: Substances, which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

Reference: EC 2001

The scientific work in this field of toxicology is followed very closely by the chemical industry, because DEHP is of great economic importance as it is the most used plasticizer in PVC having a production volume of thousands of tons per year. The present paper deals with the scientific discussions underlying the regulation and classification of DEHP with regard to the ability of the chemical to cause cancer and to impair fertility and cause developmental toxicity. This paper attempts to elucidate the degree to which the classification of DEHP has influenced the risk reduction strategy in the EU regulation of existing chemicals and predict how the present classification of DEHP will influence the management of the chemical within the framework of the new EU regulation of chemicals as proposed by REACH (Registration, Evaluation and Authorisation of Chemicals). The paper starts with a brief summary of the production, application and fate of DEHP to emphasise the importance of the case study.

2. DEHP in PVC

When PVC is formulated using DEHP, no covalent bonds between the two chemicals are made. DEHP exists as free molecules between the polymer fibres, like "peas in spaghetti". Therefore, DEHP molecules can easily leave the plastic and migrate to the surrounding environment, which could be to food wrapped in PVC folio or evaporation from vinyl floors to the air we are breathing, or it could be flushed out from car undercoating whilst the car is being washed and thereby enter the wastewater system and, in the end, the aquatic environment. Further, as DEHP is a part of blood bags, it can migrate into humans having blood transfusions. One of the most worrying scenarios is DEHP exposure during prenatal care where newborn babies are treated with devices made of PVC (Hillman et al. 1975, Tickner et al. 2001).

About 20 phthalates are used in the plastics industry. Among these DEHP is the preferred phthalate due to its excellent technical properties and its low price on the world market. In Europe, the main producers are found in Germany, Belgium, Italy and Spain. In 1997, the industries in Western Europe produced 595,000 tpa (tons per annum) and the consumption was 476,000 tpa (RAR 2001).

The amount of DEHP in PVC depends on how soft the plastic has to be. Some products can contain up to 50%, but typically there will be approximately 30% DEHP in most PVC products. Table 1 shows some products made of soft PVC containing DEHP. Many of the products are day-to-day articles that people use regularly. Some of the products such as gloves and toys come into direct contact with the skin and saliva and present possibilities for direct exposure to DEHP.

Table 1. *Different applications of DEHP*

Flooring and wall covering
Car undercoating
Cables, wires and hoses
Foot wear (e.g. shoe soles)
Clothes (print and rain clothes)
Gloves
Medical devices (e.g. tubes and blood bags)
Toys
Car interior
Tarpaulins
Furniture
Paints, printing ink and adhesives (non-polymeric application)

3. The Fate of DEHP

DEHP is released into the environment in large quantities and chemical analyses show that it can be detected in all kinds of environmental samples, such as soil, air, water or biological tissue. The total emission to the environment from the EU countries was estimated as 28,653 tons released throughout the complete life cycle of the chemical, from production through consumption and finally as waste (see Table 2).

The largest release of DEHP into the environment is about 18,000 tpa from the disposal of products (see Table 2). However, this is not surprising, as DEHP molecules are not chemically bound to the PVC matrix. Migration to the soil comes mainly from cables and PVC waste remaining in the environment.

Table 2. *Total emission (tpa) in EU of DEHP to different compartments during the total life cycle (RAR 2001).*

Emissions from	Air	Wastewater	Soil	Total
Industrial use	319	1074	74	1467
Product uses	207	2475	6559	9241
Disposal	20	2438	15487	17945
Total emission	546	5987	22120	28653

It has been calculated that approximately 4% of the quantity of DEHP can evaporate from materials such as floorings, rain clothes, toys, soles of shoes and the like, and even more can leave the products by contact with soil or water. In particular, contact with detergents can extract up to 15 % of DEHP from PVC materials. Further, wastewater from car washes can also make a considerable contribution to the emission of DEHP (Vikelsøe et al. 1998).

It could be argued that DEHP discharged into the sewerage system from households and industries will be degraded in the wastewater treatment plant. Unfortunately, this is not what happens because the microbiological processes are not one hundred percent effective and therefore the outlet of cleaned water to aquatic environment will always contain DEHP.

The fate of DEHP in the water is not fully known. However, because the chemical is lipophilic with a log Kow of 7.5 (RAR 2001), it will bind with particles and during sedimentation it will end up in marine or fresh water sediments. Having entered the sediment, the degradation of DEHP is not likely to happen because the oxygen required for the life processes of the decomposing microorganisms is not present in sediments. So, in spite of the fact that the DEHP concentration of wastewater after treatment is low, the chemical will gradually accumulate in sediments. Moreover, most DEHP entering the wastewater treatment plant will end up in the wastewater sludge, which in many countries is still used as a soil conditioner and fertilizer on agricultural fields. In Denmark, there are limit values for the concentration of DEHP in wastewater sludge (50 mg/kg dry weight) used in agriculture.
The chemical properties of DEHP, the high production volume, and the widespread use results in the presence of the chemical in biota, as well as in water, sediment, soil, air and food, and contamination will probably increase if we continue to use DEHP at the same level in the future. Therefore, it is of extreme importance to obtain valid scientific knowledge regarding the risk to the environment and health. Studies of the toxicity of DEHP are plenty, and the most controversial discussions have been those about DEHP's ability to cause cancer and to impair fertility, which will be described in the following sections.

4. Carcinogenicity

U.S.EPA classified DEHP as a probable human carcinogen based on a study published in 1982 (Kluwe et al. 1982). It was shown that lifetime ingestion of DEHP induced liver tumours in both male and female rats and mice. The study was part of the US National Toxicology Program and The International Agency for Research on Cancer (IARC) endorsed the US conclusion and decided to classify DEHP as a category 2 substance which should be regarded as if it is carcinogenic to man (EU 2001). (See Box 1 for a description of categories).

Shortly after DEHP was classified as carcinogenic, the discussion of non-genotoxic mechanisms of the cancer induction was intensified. In 1992, the WHO reviewed the studies showing that DEHP could cause hepatic peroxisome proliferation (PP) in mice and rats and thereby could have a role in "*oxidative stress and increased cell replication in the hepatocarcinogenicity of DEHP*" (WHO 1992). Further, the review stressed that the studies of PP showed dramatic species difference and that MEHP (mono-2-ethylhexyl phthalate), regarded as the most potent metabolite of DEHP, was unable to induce

PP in cultured human liver cells. In a cancer risk assessment study made by U.S.EPA (Doull et al. 1999) stated that the weight of evidence indicated that DEHP was not genotoxic and that DEHP should be risk assessed in relation to a NOAEL (No Observed Adverse Effect Level) of 20 mg/kg/day for PP. As the general exposure to human is 30 µg/kg/day, it gives a margin of safety of approximately 1000, and therefore the response in rodents was obviously not relevant to human cancer risk.

In the IARC monograph from 2000 studies on PP and epidemiological studies on cancer resulted in two findings: 1) "*there is inadequate evidence in humans for the carcinogenicity of di(2-ethylhexyl)phthalate*", 2) "*there is sufficient evidence in experimental animals for the carcinogenicity of di(2-ethylhexyl)phthalate*". The overall conclusion was as mentioned earlier that DEHP "*is not classifiable as to its carcinogenicity to humans (Group 3)*" (IARC 2000). The conclusions were based on the evidence that DEHP caused liver tumours in rodents via PP and that this mechanism could not be documented in a study with cultured human liver cells.

However, the contribution of PP to the induction of liver cancer was questioned in a comprehensive review undertaken by Melnick (2001). He wrote that the mechanistic events of the carcinogenicity of DEHP are not fully elucidated and that there could be other mechanisms in the carcinogenicity of DEHP, and he concluded that the hypothesis of DEHPs carcinogenicity during PP is not valid.

As part of the EU risk assessments of existing chemicals, the Swedish EPA evaluated the toxicity of DEHP, and it has been possible to follow the process by reading the risk assessment drafts over three different years (RAR 2000, RAR 2001, RAR 2004). In the first draft, the Swedish Rapporteur emphasised that "*although PPs may pose little risk to the population as a whole, the potential human carcinogenicity of these chemicals cannot be summarily ignored*". Further, some studies on rats showed that prenatal exposure to DEHP caused tumours in male pups, which could be due to a different mechanism than PP. The conclusion in the first draft of risk assessment (RAR 2000) was that DEHP should be classified as a category 3 carcinogen: "*Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making satisfactory assessment"*, and *"there is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2* " (EC 2001). Surprisingly, this formulation was changed to "*no classification for carcinogenicity is proposed*" in the second draft (RAR 2001), based on the same studies but for no apparent reason, and this formulation was maintained in the final version (RAR 2004). In a summary from the European Scientific Committee on Toxicity, Ecotoxicity and Environment (CSTEE 2004) giving the committees opinion on the risk assessment of DEHP, the possible carcinogenic effect of the chemical was not even mentioned.

However, a newly published paper gives support to the testicular cancer hypothesis (Voss et al. 2004). The paper describes a study of the lifelong exposure of rats to DEHP administered in food. The daily dose was 30, 95 and 300 mg/kg body weight. The histological examinations showed significantly increased tumour incidence in testes at the highest dose and a clear dose response was also demonstrated. The mechanism was different from the process of peroxisome proliferation in the liver because DEHP also induced high levels of the steroid hormones estradiol and testosterone. The new results raise the question of whether DEHP again should be classified as a substance possible carcinogenic to humans.

The studies and discussions of DEHP in relation to the classification as a possible human carcinogen show first of all that such a decision can de discussed with regard to validity of the evidence, in this case the PP hypothesis. The available studies still do not fully elucidate the mechanism of DEHP in the induction of liver cancer and not at all the induction of testicular cancer. However, it seems as the concept of PP being the explanation for the cause of cancer is very difficult to change, when a majority of the scientific community has come to such an agreement, and when the chemical industry is satisfied with a scientific statement as the PP hypothesis, there will be neither pressure from the industry and nor motivation for scientists to try to test the hypothesis.

Moreover, the case also shows that the precautionary principle has not played a prominent part in any of the risk assessments. Taking into consideration that EU recommends the use of the precautionary

principle (EC 2000) if there is lack of evidence, as there is for the PP hypothesis, it is disappointing that the principle was not even mentioned in the chapter concerning carcinogenicity in the EU risk assessment report on DEHP (RAR 2004). However, it is well known that the chemical industry has influenced the EU risk assessment reports, as many chemical associations have acted as consultants during the risk assessment procedure (SNCI 2003), and most likely they will lobby very hard to avoid a new cancer classification of DEHP.

5. Classification of DEHP as a Reproductive Toxicant

After the introduction of the estrogenic hypothesis (Sharpe and Skakkebæk 1993) saying that some environmental toxicants are responsible for disturbances in male reproduction, many chemicals were suspected of being estrogenic including the phthalates (Toppari et al. 1996). Since it was demonstrated that DEHP did not bind very well to fish estrogenic receptors and neither could it stimulate transcription of the human estrogenic receptor (Jobling et al. 1995), it was questioned if the chemical was involved in reproductive disorders at all. However, several new results have demonstrated different kinds of antiandrogenic effects of DEHP on male rats after exposure in the uterus (Gray et al. 2000, Parks et al. 2000, Moore et al. 2001, Akingbemi et al. 2004).

The story of DEHP's toxicity on reproduction could be characterised as for many other chemicals as "a story of late lessons from early warnings" (EEA 2001). As early as 1945, the first report described DEHP as having an adverse effect on rat testicles (Shaffer et al. 1945). The damage was observed as "*tubular atrophy and degeneration of the testes, resembling senile changes*" and was caused by concentra-

Table 3. Selected early studies showing adverse effects of DEHP on testicles or fertility.

Dose	Species	Exposure time	Effect on testicles	Effect on fertility	References
0.9/1.9 g/kg	Rat	90 days	tubular atrophy		Schaffer et al. 1945
0.5% in diet	Rat	3,12 and 24 month	tubular atrophy		Harris et al. 1956
250 mg/kg	Mice	6 weeks	reduced weight		Calley et al. 1966
25ml/kg i.p.	Male mice	5-12 weeks		antifertility	Singh et al. 1974
	Chick			death of embryos	Lee et al 1974
1 % in diet	Ferret	14 month	tubular atrophy		Lake et al. 1976
1-2% in diet	Rat	2,6,17 weeks	reduced weight and various histopatolgical changes	cessation of spermatogenesis	Gray et al. 1977
0.2% in diet	Female mice	18 days		embryo toxicity	Shiota et al. 1980
1-2% in diet	Rat	20 days		embryo toxicity	Tyl et al. 1988
0.1-0.15 % in diet	Mice	17 days		embryo toxicity, teratogenicity	Tyl et al. 1988

tions of 1.9 and 0.9 g/kg bw (body weight). Later, Harris et al. (1956) confirmed these findings in rats fed 0.5% DEHP in their diet. DEHP also caused reduced weight of mouse testicles at doses of 250 mg/kg body weight (Calley et al. 1966) and infertility in male mice at concentrations of 25ml/kg (internal dose) when male mice were exposed prior to mating (Singh et al. 1974). Other studies, as shown in Table 3, have confirmed these early findings. The present studies are only a small part of the available literature of the testicular toxicity of DEHP. In my opinion there was, in the late 1980s, sufficient evidence for an early warning to take action and provide studies looking more seriously at the scientific problem of testicular toxicity, but many of these problems were overlooked probably because of the ongoing discussion of the carcinogenicity of DEHP.

However, in the last decade, new and more detailed studies on DEHP exposed laboratory animals have shown that the early studies of infertility and embryo toxicity should be taken seriously. The overall conclusion of the studies has resulted in agreement that DEHP has an antiandrogenic effect leading to multiple endocrine disturbances in fetal males from exposed mothers and infertility of exposed males. In some of the studies, they exposed young male rats (Poon et al. 1997, Park et al. 2002, Akingbemi et al. 2004) and in other studies they exposed male rats *in utero* and the first postnatal days (Arcadi et al. 1998, Gray et al. 2000, Parks et al. 2000, Moore et al. 2001). Many abnormalities were detected in male rats exposed *in utero* as seen in Table 4, which gives a summary of the findings. It seems as though perinatal exposure causes the most serious disturbances in male rats. Further, it is thought provoking

Table 4. A summary of detected abnormalities in the reproductive organs of male rats after exposure to DEHP.

Abnormalities in DEHP exposed male rats	References
Histological damage in testes	Poon et al. 1997[a] , Gray et al. 2000[b], Parks et al 2000[b], Moore et al. 2000[b], Park et al. 2002 [a]
Weight reduction of testes	Poon et al. 1997[b], Arcadi et al. 1998[b], Gray et al. 2000[b], Parks et al. 2000[b], Moore et al. 2000[b], Park et al. 2002[a]
Shortened anogenital distance	Gray et al. 2000[b], Parks et al. 2000[b], Moore et al. 2001[b], Borch et al. 2004[b]
Female like nipples	Gray et al. 2000[b], Moore et al. 2000[b], Borch et al. 2004[b]
Reproductive malformations (undescended testicles, hypospadia)	Gray et al. 2000[b], Moore et al. 2000[b]
Reduction in testosteron production (perinatal exposure)	Parks et al. 2000[b], Moore et al. 2000[b] ,Borch et al. 2004[b]
Increase in serum testosterone/estradiol and Leydig cells (long-term exposure)	Akingbemi et al. 2004[a]
Disturbed sexual behaviour	Moore et al. 2000[b]

a) exposed young males b) exposed *in utero*

that DEHP is able to induce the same abnormalities (hypospadias, cryptorchidism and testicular cancer) observed to increase in human populations (Toppari et al. 1996, Jensen et al. 2004). Hypothesizing that DEHP could be involved in the decline in male fertility, it would be the exposure of male foetus of pregnant women that is of highest concern.

Effects of DEHP on female rats have also been detected. In a review (Lovekamp-Swan and Davis 2003) a model was presented, suggesting that DEHP's main metabolite MEHP (mono-2-ethylhexyl phthalate) suppresses the production of estradiol in the ovary leading to anovulation. Suspicion of phthalate effects in human females, was presented by Colon et al. (2000). They showed that young girls from Puerto Rico with premature breast development had blood levels of DEHP correlating significantly with the abnormalities. Although, the sample size was low (41 patients and 35 controls), the study adds to the huge evidence of an endocrine disrupting activity of DEHP.

In a new study undertaken by Swan et al. (2005) where they evaluated anogenital distances (AGD) in baby boys, it was found that a short distance, expressed as anogenital index, correlated inversely with levels of phthalate metabolites in urine sampled from mothers during pregnancy. In spite of that, MEHP could not be associated with the anogenital effects, two other metabolites of DEHP, respectively MEOHP (mono-2-ethyl-5-oxohexyl phthalate) and MEHHP (mono-2-ethyl-5-hydroxyhexyl phthalate) were shown to correlate on the borderline of statistical significance. Compared to rat studies showing decreased AGD in male pups after maternal DEHP exposure, it was discussed that this difference in effects of DEHP or its metabolites could be due to the study's small sample size, or it could be explained as a species difference between rats and humans in their response to DEHP.

Even though the evidence from humans is not convincing so far, the results from the studies presented here are in agreement with the earlier mentioned conclusion emphasizing that DEHP can act in male rats as an antiandrogenic substance. However, effects of DEHP on females are not fully elucidated.

In conclusion, the weight of evidence justifies the classification of DEHP among substances "*which should be regarded as if they impair fertility in humans*" and "*which should be regarded as if they cause developmental toxicity to humans*", as described for substances toxic to reproduction in category 2 (EC 2001). (See Box 2 for a description of categories).

6. The Chemical Industry's Response

The decision to classify DEHP as a substance that most probably can cause reproductive toxicity in humans was not popular in the chemical industry. Shortly after the classification, the European Council for Plasticizers (ECPI 2002-2004) proclaimed that the "classification of DEHP is unjustified" because DEHP has been used without harm for more than 40 years. They referred to a study by Kurata et al. (1998) where primates exposed to DEHP did not show the effects on testicles that had been seen on rats and mice. These differences between species were used as an argument for another classification (category 3) because these primates are biologically closer to humans than rats, it would be expected that DEHP does not induce damage to the human male testicles. However, the primate study was carried out with adult animals of 12 to 15 months contrary to the rat studies, where the exposure took place in utero, known as the most sensitive phase of exposure because the gonads are developed in this period.

When reading the ECPI homepage (http:www.dehp-facts.com), it is obvious that the organization follows the DEHP risk assessment procedure very closely. So, ECPI welcomed the EU decision that gave "EU Member States more time to consider important new research findings which could have significant effect on the Risk Assessment of di-(2-ethylhexyl) phthalate" (ECPI 2002-2004). In press releases, the ECPI has been eager to describe studies that can counter the evidence that DEHP is hazardous to humans. To convince the scientists that DEHP is not toxic to reproduction in man, ECPI again paid attention to a new study on primates (Tomonari et al. 2003). In the study, young primates aged 3 to 15 months, were exposed to DEHP, and no effects on testis were detected, contrary to the rat studies. However, the value of this study as reverse evidence is weak, because it is now quite clear that the most sensitive moment of male exposure is in uterus during pregnancy and not 3 to 15 months after birth.

Box 2

Criteria for Classification of Chemicals Toxic for Reproduction

Category 1: Substances known to impair fertility in humans. There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

Substances known to cause developmental toxicity in humans. There is sufficient evidence to establish a causal relationship between exposure to the substance and subsequent developmental toxic effects in the progeny.

Category 2: Substances, which should be regarded as if they impair fertility in humans. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of: clear evidence in animal studies of impaired fertility in the absence of toxic effects, or evidence occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of the other toxic effects – or other relevant information.

Substances which should be regarded as if they cause developmental toxicity to humans. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity generally on the basis of: clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects – or other relevant information.

Category 3: Substances which cause concern for human fertility. Generally on the basis of: results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in category 2 – or other relevant information.

Substances which cause concern for humans owing to possible developmental toxic effects. Generally based on: results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in category 2 – or other relevant information.

Reference: EC 2001

ECPI also drew attention to a new investigation of teenagers, highly exposed when babies to DEHP from medical devices. The study did not show any kind of adverse effects in pubertal development and no change in the levels of sex hormones was seen (Rais-Bahrami et al. 2004). The group of teenagers was of 13 males and six females, which one could argue is a relatively small group on which to draw conclusions. Furthermore, it is important to note that the authors of the paper hypothesize that the lack of effect could be due to a lack in the metabolism of the fetus converting DEHP to MEHP, which is supposed to be the active metabolite. This leads to the hypothesis that *in utero* exposure to DEHP can harm the human male fetus by a process where the maternal metabolism is transforming DEHP to MEHP.

Another argument from the industry, normally used to acquit substances of causing damage to humans, is "no exposure – no harm". The meaning of this argument is that no matter how hazardous DEHP is, it will only harm humans if they are exposed to the substance above the hazard levels. Therefore, it is necessary to know the exact exposure of the public or individuals before any risk of DEHP can be evaluated. The need for knowledge of exposure is part of the risk assessment concept, which is fully agreed by the EU authorities, and described in the Technical Guidance Document on Risk Assessment (ECB 2003). However, to ask for exposure data will often delay the risk assessment and then postpone any decision of restriction or ban of the chemical, and in that way the industry obtains more time to produce and earn money. Further, it is difficult to calculate exposure levels for all kinds of scenarios and this adds a great deal of insecurity to the risk assessment. It is therefore clear that using the exposure levels as part of the risk assessment is in favour of the industry.

7. The Risk of DEHP

The principles of risk assessment can be described in three steps: 1) hazard identification, including dose response assessment, 2) exposure assessment and 3) risk characterization. An important part of hazard identification (step 1) is to find the No Observed Adverse Effect Level (NOAEL). The level is derived from animal studies of the most sensitive species and for the most sensitive effects. The value refers to the highest dose observed where no effects were seen. The exposure assessment (step 2) is rather complicated, particularly for a compound with such a widespread use as DEHP. However, evaluation of DEHP exposure has already been done during a lot of assessment programmes. The EU risk assessment report on DEHP (RAR 2001) shows exposure data for workers, adults and child consumers and for medical treated persons. These data are used for the risk characterization (step 3) where NOAEL from animal studies are compared with exposure levels for humans thus providing the value called margin of safety (MOS). An example of such a calculation can be seen in Box 3. If a chemical is characterized with a MOS value lower than 100, it means that there is a risk and it will result in some kind of action for the particular scenario.

Box 3

Calculation of MOS, margin of safety, for effects on testes for children exposed to DEHP. The two set of data needed are the NOAEL and the exposure level. Both set of data are from the EU risk assessment report on DEHP (RAR 2004).

NOAEL, No Observed Adverse Effect Level was determined from rat studies to be:

4.8 mg/ kg body weight

The exposure level for children playing with PVC toys and other exposure pathways was calculated to be:

0.234 mg/kg body weight

MOS: 4.8/0.234 = 20.5

The industry really has a great interest in these risk calculations. In the case of DEHP, they have tried to introduce a very high NOAEL for effects on testes. According to the ECPI press release (06 March 2002), the NOAEL was claimed to be 100 mg/kg body weight per day in rats, estimated from a multi-generation study of Wolfe et al. (2002). Surprisingly, the EU scientific committee on toxicity (CSTEE 2004) newly concluded that the NOAEL, which should be used in the risk assessment of testicular toxicity, should be 4.8 mg/kg body weight per day, based on the same study by Wolfe et al. (2002). With the NOAEL of 100 mg/kg proposed by the chemical industry (ECPI 2002-2004), the MOS will become very high and there would be no risk at all for effects on testes. So far, the industry has not proposed lower exposure levels for children than calculated by the EU experts, even though this value is the one which could be really questioned because it is often described as the most uncertain parameter in the risk assessment.

Because DEHP belongs to the group of high production volume chemicals, it has a high priority regarding risk assessment, and in 1995 it was included on the priority list No. 2 of chemicals in the European Unions programme of risk assessment of

existing chemicals (Com1995). In the Swedish risk assessment report concerning DEHP, its hazardous properties are described with testicular toxicity and developmental toxicity as the most critical endpoints. The risk evaluation procedure focuses on both hazardous effects and exposure and describes the interaction of these two parameters in various scenarios where the margin of safety (MOS) is calculated. For the calculation of the MOS, the NOAEL of DEHP effect on testes and development are used and divided with the level of exposure (see Box 3). In a scenario with workers exposed to DEHP during industrial use, the exposure level was 1.36 mg/kg bw/day for (dermal and inhalation) (RAR 2001). When using a NOAEL of 4.8 mg/kg bw/day MOS can be calculated to be 3.5 (4.8/1.36) showing a high risk for workers. For children exposed to toys and child-care articles, the exposure was calculated to 0.2 mg/kg bw/day (RAR 2001), and the MOS value of 24 (4.8/0.2) is still too high to eliminate the risk of testicular damage in boys. The requirement of a MOS-value lower than 100 is based on the consideration of a variety of uncertainness, and should protect the most susceptible humans and take into account that humans could be more sensitive than laboratory animals just to mention two important uncertainties. So the risk assessment clearly shows that DEHP exposure constitutes a considerable risk for male workers and also a risk for boys.

8. DEHP in the Light of REACH

The proposal of a new chemical law in EU, the so-called REACH (Registration, Evaluation and Authorisation of CHemicals) was introduced in 2001 (Com 2001). The first reading of the final version (Com 2003) was finished in 2005. The second and third reading will probably be completed during 2006 and the law is expected to be in force not earlier than 2007. Further, it will take 11 years before it is finally implemented. It is expected that the new law will lead to firmer regulation of chemicals in Europe. In particular, the so-called CMR substances, which are *c*arcinogenic, *m*utagenic or *r*eproductive toxicants, will be regulated more strictly than they are under the present EU regulation. If a CMR substance is characterized as a CMR chemical in category 1 or 2 (but not category 3) it should be part of the authorisation system and will therefore not be allowed to be used without a specific authorisation for a specific use. So, only if it is supposed that a CMR chemical is indispensable or its use is very important, will an authorisation be given. Therefore, the implementation of REACH can be very unpleasant and expensive for an industry producing chemicals characterized as toxic for reproduction in category 2 as in the case of DEHP.

When, in the future, REACH is implemented, it will result in either a ban of DEHP or a long list of different authorizations in relation to the widespread use of the chemical. Whether, the regulatory authorities might find that DEHP is indispensable or not, is an extremely important question. Taking into consideration that it has taken years for the EU Commission to recommend some restrictions on DEHP, it will probably also be a battlefield between the environmental authorities and the chemical industry lobby as to when this chemical is going to be regulated based on the REACH proposal.

9. Discussion

Obviously, it has taken quite a long time from the early warnings of the hazardous effects of DEHP first appeared until some actions were taken. Further, the first action taken in this case, namely to classify DEHP as possibly carcinogenic to humans, was later changed to "regarded as if it is not carcinogenic to man". In spite of the fact that in 1982, IARC and USEPA classified DEHP as probably carcinogenic to humans, it was never accepted by the EU authorities, and DEHP was not classified as toxic at all and could not be found on the EU list of dangerous chemicals. First in 2001, when it was classified as a reproductive toxicant as a category 2 was it placed on the list and will now be labelled with the risk phrases R60 "may impair fertility" and R61 "may cause harm to the unborn child" when brought onto the market (EU 2001).

Minimizing risk is an important purpose of risk assessment. During the 1980s a lot of energy was used to reduce exposure to carcinogenic chemicals. The reason for this preference was the consensus among scientists that in theory no limit value can be set for carcinogenic effects, because one molecule of a chemical can harm DNA and start the initiation of cancer, and therefore such chemicals should be banned or phased out over time. However, if the mechanism of cancer induction can be proved to be non-genotoxic, and therefore not involving interaction with DNA, it is possible to set limit values,

and so NOAEL can be part of the risk reduction strategy which is less stringent than for genotoxic chemicals. When DEHP peroxisome proliferation was chosen as the explanation of liver cancer in rats, it could be seen as being in favour of the industry, because it made it possible to argue for "no risk" if the exposure is below the hazardous levels (MOS higher than 100).

The classification of DEHP as toxic for reproduction resulted in demands for labelling with risk and safety phrases and also started the discussion of risk reduction strategies involving the use of NOAEL and exposure levels for the risk characterization. Regarding the labelling, it is worth mentioning that the risk and safety phrases will only be on packages of the pure chemical. For that reason, consumers will not be warned when using PVC or other products formulated with DEHP. However, some consumer protection has already been initiated in/by the EU: DEHP is forbidden in toys for children of less than three years, and there are limit values for migration to food from wrapping folio, and it is also recommended not to use PVC containing DEHP in utilities for neonatal care.
The risk assessment of DEHP started as early as 1995 and the EU Commission has not yet finished the work. The Swedish National Chemicals Inspectorate published a risk reduction strategy in 2003 (SNCI 2003) based on the 2001 risk assessment report (RAR 2001). The recommendations are only based on the classification of DEHP as toxic for reproduction and development, and they point out that experts are still not in agreement about the NOAEL for testicular toxicity and that information is missing regarding all sources of emissions and lifetime exposure.

For consumers they recommend that "the interimistic ban on the use of DEHP in toys and childcare articles should be secured and broadened to cover all such items that could be put into the mouth of a child and that intended also for children above 3", and the use of DEHP in packaging material for fatty food should be restricted. Further, they propose that DEHP in medical devises giving rise to exposure of neonates should be banned or restricted. Finally, they stress that the new legislation for chemicals will create an authorization procedure for CMR chemicals and this will include DEHP resulting in time limits for authorised use.

It seems that more restrictions of the use of DEHP can be expected in the future, and unless the classification is changed, the application of DEHP will probably be reduced greatly or be phased out. Even without full and clear evidence, a strict risk reduction strategy could be justified with reference to the precautionary principle (EU 2000) according to which the principle should be used where 1) the scientific knowledge is insufficient and 2) where the expected hazards are very serious. In my opinion, this could be said for the DEHP: 1) there is a lack of knowledge in the epidemiological evidence of its hazardous effect on humans and 2) the expected hazard on human reproduction belongs to the most serious problems for the future generations.
The main conclusion of the present paper is that the classification in relation to the application of the authorization concept in REACH will be much more important than earlier. Therefore, it can be expected that the chemical industry will increase their lobbyism in general and open discussions of those scientific papers dealing with mechanisms of carcinogenicity and reproduction toxicity in a search for arguments to avoid classifications of chemicals as CMR substances in category 1 or 2. However, the regulation of chemicals as a trade-off between industry and authorities always results in a delay that is in favour of the industry. Every day without restrictions means that a chemical such as DEHP is produced in huge amounts. Subsequently, it can result in a widespread use in a lot of products leading to uncontrolled environmental health problems.

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